In the Final Office Action dated October 18, 2002, the Examiner has withdrawn rejections from the previous Office Action. However, the Examiner maintained a number of rejections. The currently pending rejections are:

1) Claims 21 and 32 stand rejected under 35 U.S.C. §102(b); and

2) Claims 21 - 41 stand rejected under 35 U.S.C. §103(a).

Claims 21-41 are cancelled herein, rendering these rejections moot. Applicant believes that the pending Claims are not taught or suggested by the prior art, and that the Examiner has failed to establish a *prima facie* case for obviousness of the pending claims. Therefore claims 42-73 should be passed into allowance.

I. THE CLAIMS ARE NOT ANTICIPATED

The Examiner has rejected the claims as allegedly anticipated by one reference (Bidwell *et al.*). The Federal Circuit has stated the relevant analysis for anticipation as follows:

> "A claim is anticipated only if each and every element as set forth in the claims found, either expressly or inherently described, in a single prior art reference."[1]

Applicant respectfully submits that Bidwell *et al.* does not teach each element of the claims.

I.a. Bidwell *et al.* Does Not Anticipate the Claims

Claims 21 and 32 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bidwell and Hui (hereinafter "Bidwell"). Applicant respectfully disagrees. Bidwell teaches HLA-DR/Dw allotype matching based upon polymerase chain reaction (PCR) amplification of HLA-DRB gene exon 2 nucleotide sequences before a kidney or bone marrow transplantation procedure can be scheduled.

The Examiner argues " . . . the definition of "scheduled for surgery" may encompass both the interpretation that scheduled means a time, date and place for surgery or may also mean more generically, scheduled for surgery pending the appropriate transplant match." (Office Action

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[1] *Verdegall Bros. v. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

10/18/2002, page 3). The Examiner is in error. Cancelled claim 21, and added claim 42, recite "a patient scheduled for a surgical procedure", not "a patient scheduled for surgery pending the appropriate transplant match" or a patient "identified for surgery" as the Examiner impugns. To the contrary, applicant asserts that the intended meaning of "scheduled" is perfectly clear i.e. "To plan or appoint for a certain time or date." (The American Heritage Dictionary, Houghton Mifflin Co., Boston, 2nd College Edition, 1985.). Bidwell cannot anticipate the present claims because, lacking a suitable transplantation match, no surgery is scheduled.

In addition, the Examiner argues "It is noted that neither Claims 32 nor 37 have any requirement that the "surgery must be scheduled". Therefore, the term perioperative as provided in the specification clearly encompasses when surgery is first contemplated." (Office Action 10/18/2002, page 4). The Examiner is in error. Cancelled Claim 32, and added Claim 55, recite "subjecting said subject to a surgical procedure." Cancelled Claim 37, and added Claim 62 recite "determining a risk for complications during a surgical procedure." Conversely, it is not necessary that a surgical procedure be performed to practice Bidwell. Thus, Bidwell does not teach the element that a surgical procedure take place at a certain time or date.

In order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended cancelled claims 21 – 41, and added claims 42, 51-53, 55, 59-62, and 67-69 reciting "in two or more genes". The Examiner concedes Bidwell does not teach detection of two or more nucleic acid markers in two or more genes:

> "None of the cited references specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures." (Office Action 10/18/2002, page 21).

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

II. THE CLAIMED INVENTION IS NON-OBVIOUS

The Examiner has rejected the claims as allegedly being obvious in view of a number of references. None of these references, alone or in combination, teach or suggest generation of a genomic profile for use in selecting a perioperative course of action. None of these references, alone or in combination, teach or suggest generation of genomic profiles for use in selecting a surgical procedure treatment course of action. None of these references alone, in combination, or in combinations of combinations, teach or suggest detecting two or more genetic markers in two or more genes clinically associated with two or more conditions for use in the perioperative interval.

Applicant asserts that the Examiner has not met the burden of establishing a *prima facie* case of obviousness. *Prima facie* obviousness based on a combination of references requires that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references."[2] "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence"."[3] The suggestion to combine prior art references must come from the cited references, not from the applicant's disclosure.[4]

The Examiner recognizes "None of the cited references specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures." (Office Action 10/18/2002, page 21). To make up for this deficiency the Examiner cites Miller in a series of combinations with other references e.g. Quane. The Examiner then concludes: "Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, as taught by Quane." (Office Action 10/18/2002, page 6). To the contrary, in the present application, the claims all recite testing two or more nucleic acid markers, in two or more genes, to generate a

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2 *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

3 *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

4 *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1998)

genomic profile for use in the perioperative interval. The Miller reference does not mention even one of these limitations, giving no instruction for genomic testing whatsoever, or of the particular criteria necessary to select the genomic markers to one of ordinary skill in the art.

Because of the absence of this information from Miller, as well as the absence of even a suggestion of using genomic testing in the perioperative interval, it is improper to combine Miller with any other art. Since the primary reference cannot be properly combined, there is no *prima facie* showing of obviousness. Nor, as obligated by law, has the Examiner's burden been met with clear and convincing evidence of obviousness in the form of a reference, affidavit, declaration or anything other than the Examiner's conclusory guesses.

As set forth in *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."
>
> Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant."

The Examiner's statement of rejection does not establish the requisite suggestion in the art to combine elements disclosed in the prior art. "A rejection cannot be predicated on the mere identification . . . of individual components of claimed limitations. Rather, <u>particular findings</u>

must be made as to the reasons the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."[5]

Instead, the Examiner has concocted an argument for rejection on the basis of obviousness by coupling assertions of the invention's clear-cut and undisputed utility, with incorrect, unsupported and conclusory guesses-in-hindsight about what an ordinary artisan "would have clearly recognized" or "would have been motivated to do". The Examiner's guesses do not satisfy requirements for establishing the *prima facie* case of obviousness. The only source available to the Examiner teaching these assertions is the present disclosure.

To assist the Examiner, the Applicant has put forward objective, specific and ample evidence showing the Examiner's inability to fabricate a *prima facie* case of obviousness. In the Office Action of October 18, 2002 the Examiner has perfunctorily dismissed, but not contradicted, this evidence. As detailed above, it is a matter of law that to sustain the rejection the Examiner must put forth actual evidence. Instead, the Examiner has inappropriately concluded that because the invention is very useful, it must therefore be obvious. However, the Examiner cannot rely on gut feelings or personal beliefs no matter how strongly the Examiner holds these convictions. On the current evidence of record the Examiner's rejections cannot stand. If the required evidence is not provided and the rejections are sustained, the Examiner will be unfairly and inappropriately delaying allowance of the present case. For these reasons Applicant respectfully requests that the rejections be withdrawn.

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5 *Ecolochem*, 227 F.3d, 1361, 1375, 56 USPQ2d 1065, 1076, quoting *Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317.

CONCLUSION

All grounds of rejection of the Final Office Action of October 18, 2002 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 1/8/03

David A. Casimir
Registration No. 42, 395

Medlen & Carroll, LLP
101 Howard Street, Suite 350
San Francisco, California 94105

APPENDIX I

SHOWING MARKED UP VERSION OF CLAIMS

42. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure.

43. The method of Claim 42, wherein said course of action comprises administration of anesthesia during a surgical procedure.

44. The method of Claim 43, wherein said surgical procedure is non-invasive surgery.

45. The method of Claim 43, wherein said surgical procedure is invasive surgery.

46. The method of Claim 42, wherein said course of action comprises administration of anesthesia during a medical procedure.

47. The method of Claim 42, wherein said genomic profile comprises information pertaining to a pharmacodynamic risk.

48. The method of Claim 42, wherein said genomic profile comprises information pertaining to a pharmacokinetic risk.

49. The method of Claim 42, wherein said genomic profile comprises a presymptomatic diagnosis.

50. The method of Claim 42, wherein said genomic profile comprises information pertaining to differential diagnosis of co-existing diseases.

51. The method of Claim 42, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes, said genes selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2*, *F5*, *RYR1*, *CACNA1S*, and *CPT2*.

52. The method of Claim 51, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes.

53. The method of Claim 51, where in said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes.

54. The method of Claim 42, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

55. A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) providing a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes known to be associated with perioperative phenotypes to generate a genomic

profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure.

56. The method of Claim 55, wherein said genetic markers are associated with a pharmacological response.

57. The method of Claim 56, wherein said pharmacological response is to an anesthetic.

58. The method of Claim 56, wherein said pharmacological response is to drugs used in anesthetic practice.

59. The method of Claim 55, wherein said two or more nucleic acid genetic markers comprises a mutation in two or more genes, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2.*

60. The method of claim 59, wherein said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

61. The method of claim 59, wherein said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

62. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency, impaired debrisoquine metabolism, thrombosis, and malignant hyperthermia to generate a genomic profile,

wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

63. The method of Claim 62, wherein said course of action comprises administration of anesthesia during a surgical procedure.

64. The method of Claim 63, wherein said surgical procedure is non-invasive surgery.

65. The method of Claim 63, wherein said surgical procedure is invasive surgery.

66. The method of Claim 62, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

67. The method of Claim 62, wherein the said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

68. The method of Claim 62, wherein the said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

69. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject; and

c) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency and impaired debrisoquine metabolism to generate a genomic profile, wherein said genomic profile provides

information for use by a physician in determining a risk for complications during a surgical procedure.

70. A method for selecting an appropriate anesthesia treatment during surgery, comprising:

d) providing a sample from a perioperative subject; and

e) subjecting said sample to an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said markers are known to be associated with an adverse response to anesthesia treatment;

f) subjecting said subject to a surgical procedure, wherein said assay results are consulted in selecting an appropriate anesthesia treatment for said subject.

71. The method of Claim 70, wherein said selecting comprises selection of dosages of anesthesia.

72. The method of Claim 70, wherein said selecting comprises selection of anesthesia compounds.

73. The method of Claim 70, wherein said selecting comprises selection of monitoring procedures.